Remarks

I. Status of the Application and Claims

As originally filed, the present application had a total of 23 claims. All of these, except claims 12-16 were cancelled as the result of a restriction requirement. New claims 24-30 have been added herein. Thus, the claims presently pending in the application are 12-16 and 24-30.

II. The Amendments

The specification of the application was amended to correct a reference to a prior case relied upon for priority.

New claims 24-30 have been added. Support for claims 24-29 may be found on page 2 of the application, lines 8-20. Support for new claim 30 may be found on page 3 of the application, lines 30-33.

None of the amendments described above add new matter to the application and their entry is therefore respectfully requested.

The Rejections

On pages 2-4 of the Office Action, the Examiner rejects all pending claims under 35 U.S.C. § 103 as being unpatentable over Shaish, *et al.* (*J. Clin. Invest. 96*:2075-2082 (1995)) either alone or in combination with Samokyszyn, *et al.* (*J. Biol. Chem. 262*:14119-14133 (1987)). It is alleged that Shaish teaches that all-trans isomers of beta-carotene inhibit the formation of atherogenic lesions and that metabolites of this compound inhibit atherosclerosis. Although Shaish does not teach the forms of retinoic acid recited in Applicants' claims, the reference by Samokyszyn is cited as showing that oxidized forms of retinoic acid are active. As a result, the Examiner alleges: "Accordingly, one of ordinary skill in the art would have used oxidized retinoic (cis as well as trans) in the teachings of Shaish, with an expectation to inhibit lipid peroxidation and in turn inhibit atherosclerosis."

Applicants respectfully traverse this rejection.

The reference by Shaish describes a study in which beta-carotene was administered to rabbits on a high-cholesterol diet to determine its effect on oxidative damage to LDL and whether it inhibited atherosclerosis. The authors concluded that the beta-carotene did, in fact, prevent atherosclerosis but that this effect was unrelated to the oxidation of LDL. Thus, in the abstract of the reference, the authors state:

> The effect of all-trans beta-carotene on atherogenesis can thus be separated from the resistance of LDL to oxidation, indicating that other mechanisms may account for the ability of this compound to prevent vascular disease. Our results suggest that metabolites derived from all-trans beta-carotene inhibit atherosclerosis when hypercholesterolemic rabbits, possibly via stereospecific interactions with retinoic acid receptors in the artery wall.

It is therefore not a generalized type of scavenging activity that appears to account for the effects observed by Shaish, but rather a specific receptor-ligand interaction. Interactions of this type tend to be relatively sensitive to changes in ligand structure and, although the authors suggest that one or more metabolites of beta-carotene are responsible for the effects observed, one could not reasonably draw the conclusion that any specific metabolite represented an active compound. In this regard, it should be noted that the metabolism of beta-carotene is quite complex (see, *e.g.*, the Samokyszyn reference cited in the Office Action) and Shaish provides no teaching that would allow one to preferentially look for one type of metabolite rather than another. Also, Applicants see nothing in the Shaish reference that would require that the metabolite responsible for the activity observed would need to be a *direct* breakdown product of beta-carotene. In other words, a metabolic product of beta-carotene could undergo further processing to generate an additional metabolite or metabolites responsible for the effects observed.

In light of the above considerations, Applicants respectfully submit that the Shaish reference may provide an incentive for a researcher to initiate experiments in which they

search for a relationship between the breakdown products and metabolites of beta-carotene and atherosclerosis, but the number of possible alternatives is very large and success could not be assured (especially if the responsible metabolite was a secondary product). There is nothing in the Shaish reference that would lead one of skill in the art to select any of the compounds recited in the present claims. In light of these considerations Applicants submit that a *prima facie* obviousness has not been established.

The Office Action indicates that the Samokyszyn reference teaches that active forms of retinoic acid are oxidized. The only possible suggestion of this nature that Applicants can find in the reference appears in the third full paragraph in column 1 on page 14129. In this paragraph, the authors refer to a scientific article by Wertz, *et al.* where it was suggested that an oxidized form of retinoic acid may be responsible for inhibiting TPA-induced tumor formation. Thus, the suggestion regarding oxidized forms of retinoic acid appears to be very limited in scope and does not extend to atherosclerosis. Moreover, the Samokyszyn authors question whether the Wertz article was, in fact, correct in its conclusions. Thus, they state:

> Our observation that the 5,6-epoxide is generated via addition reactions involving retinoid-derived or unsaturated fatty acid-derived peroxyl radicals suggests that the hydroperoxide-dependent cooxidation of 13-*cis*-retinoic acid by PGH synthase may represent a form of metabolic activation. However, 5,6-dihydroretinoic acid, which is saturated in the 5,6 position, also displays anti-TPA activity, although it is less active than the 5,6-epoxide. Thus, the significance of epoxidation in retinoid-dependent chemopreventive activity is currently unclear.[1]

In light of the above, Applicants respectfully request that the Examiner reconsider whether the Samokyszyn reference, when fairly considered, actually teaches or suggests that oxidized forms of retinoic acid may be active in preventing atherosclerosis.

Although it is not entirely clear from the Office Action, it appears that the basis for combining Samokyszyn with Shaish may be that the Examiner believes that the former

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[1] Page 14129, first column, last 3 sentences of the third full paragraph. Citations were omitted.

teaches that oxidized forms of retinoic acid should be active in inhibiting lipid peroxidation. For example, the Office Action states on page 4:

> Accordingly, one of an ordinary skill in the art would have used oxidized retinoic (cis as well as trans) in the teachings of Shaish, with an expectation to inhibit lipid peroxidation and in turn inhibit atherosclerosis.

However, as discussed previously, the Shaish reference actually suggests that lipid peroxidation is unrelated to the effects observed using beta-carotene. Thus, such an effect cannot be relied upon as a viable motivation for combining references.

Finally, the Samokyszyn reference contains no suggestion whatsoever that oxidized forms of retinoic acid represent the only active form of these compounds, that the oxidized forms of retinoic acid are important in atherosclerosis, or that would lead one of skill in the art to select the compounds recited in Applicants' claims as being responsible for the activities observed by Shaish. Thus, Applicants respectfully submit that the Samokyszyn reference does not cure the basic defects of Shaish mentioned earlier and that, even if one were to combine the references, they would not arrive at the method presently claimed by Applicants.

Conclusion

In light of the amendments and discussion above, Applicants submit that the Examiner's rejection of claims under 35 U.S.C. § 103 has been overcome. It is therefore respectfully requested that this rejection be withdrawn and that the claims presently pending in the application be allowed.

If in the opinion of the Examiner a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (202) 419-7013.

Respectfully submitted,

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Appendix

Version with Markings to Show Changes Made

The paragraph on lines 5-6 on page 1 of the application was amended herein. The changes that were made to the paragraph are shown below with the bracketed words indicating text that was removed.

> The present application claims the benefit of U.S. provisional application numbers 60/228,763, filed on August 30, 2000 [(pending)], and 60/246,067, filed on November 7, 2000 [(pending)].